Clinicopathologic Conference

Dementia and Ataxia in a Patient With AIDS

Discussants
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HARRY V. VINTERS, MD:* This 29-year-old homosexual man had a history of multiple sexual partners, one of whom had died of acquired immunodeficiency syndrome (AIDS) and the clinical diagnosis of AIDS encephalopathy—that is, progressive dementia terminating in coma. His medical history included an episode of hepatitis and treatment at a drug rehabilitation center two years previously. The patient was in his usual state of good health until about 18 months before he died, when he noted white spots on his tongue; biopsy specimens were taken and showed hairy leukoplakia. At about the same time, he noted fevers and sweats, and, based on abnormal helper:suppressor cell ratios in his peripheral blood, the diagnosis of AIDS-related complex was made (November 1984). He was treated at UCLA Medical Center (August 1985) for shortness of breath caused by *Pneumocystis carinii* pneumonia. Thereafter, he noted persistent fevers. Beginning six to seven months before his death, the patient noted decreased mental function, and this gradually progressed to severe dementia and cerebellar ataxia. He was incapable of walking without assistance for the final six months of his life. Four months before he died, he was admitted to hospital for dyspnea not obviously caused by *Pneumocystis* infection. A computed tomographic (CT) scan of the head showed mild cerebral cortical atrophy.

On physical examination in the outpatient clinic three months before death, he appeared ill and wasted and had profound dementia. His blood pressure was 114/90 mm of mercury and heart rate 84 per minute. No funduscopic abnormalities were noted. The oropharynx showed a yeast infection. A large external nasal lesion consistent with Kaposi's sarcoma was present. Coarse rhonchi were detected throughout both lung fields. There was no peripheral edema, organomegaly or lymphadenopathy. On neurologic assessment he had, in addition to dementia, diffuse hyperreflexia with pronounced clonus of the right arm and leg. Diminished motor strength was noted in all flexor muscles, but extension was normal. He had positive palmomental and glabellar reflexes. Detailed sensory testing could not be carried out. For the remaining weeks, he was cared for by friends at home, where he died in June 1986. His mentation was said to show progressive decline over that time interval.

GREGORY L. CLARK, PhD, MD:* In summary, we are presented with a 29-year-old homosexual man with documented AIDS manifested by the opportunistic infection *P carinii* and Kaposi's sarcoma. He also suffered neurologic complications including severe dementia, cerebellar ataxia, peripheral neuropathy and diffuse weakness in joint flexors. A CT scan done about four months before death showed only mild cerebral cortical atrophy.

For the purposes of this discussion, I shall assume that the dementia referred to in the case presentation is that of persisting cognitive impairment in the absence of significant toxic-metabolic disturbance.

The differential diagnosis of central neurologic complications in a patient with AIDS is quite long, but encompasses viral syndromes, nonviral infections, neoplasms and, less frequently, stroke.[1] Viral syndromes include the recently defined AIDS-dementia complex,[2,3] aseptic meningitis, herpes simplex encephalitis, progressive multifocal leukoencephalopathy, varicella zoster encephalitis and viral myelitis. Nonviral infections include toxoplasmosis, cryptococcosis, candidiasis, aspergillosis, coccidioidomycosis, infection by atypical mycobacteria, tuberculosis and bacterial infections. Neoplasms involving the central nervous system (CNS) include primary lymphoma, systemic lymphoma with brain involvement and Kaposi's sarcoma.

In this case, we can narrow the differential diagnosis by considering that the CT scan showed no focal lesions but only mild cortical atrophy. Progressive multifocal leukoencephalopathy typically presents with characteristic low-density lesions on CT. Toxoplasmosis almost invariably presents with one or more ring-enhancing lesions. In rare instances, however, there have been cases of documented toxoplasmosis with a normal CT scan.[4] In eight recently reported cases of

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CMV = cytomegalovirus
CNS = central nervous system
CSF = cerebrospinal fluid
CT = computed tomography
HIV = human immunodeficiency virus

primary CNS lymphoma,[1] the CT scans were normal in three cases, there was homogeneous enhancement in one and there were hypodense areas with peripheral enhancement in four. Metastatic Kaposi's sarcoma to the brain is extremely rare, but a focal lesion was seen in one patient in whom a scan was done.[5] Fungal infections might be expected to present with nonfocal CT findings. CT scans of AIDS patients with cryptococcal infection may show cerebral atrophy or hydrocephalus or may be entirely normal.[1] Information regarding the CT presentation of the remaining fungal infections in AIDS patients is unavailable. CNS tuberculosis could be expected to present with basal enhancement on the CT scan.

The presentation of herpes simplex encephalitis in patients with AIDS has been shown to follow a spectrum ranging from subacute encephalitis with a normal CT scan to a hemorrhagic necrotizing encephalitis. Finally, the so-called AIDS-dementia complex, felt by some to reflect direct cerebral infection by the human immunodeficiency virus (HIV),[2,3] often presents with cortical atrophy, but white matter attenuation is noted in some patients, and in one case a periventricular white matter lesion was seen.[2]

Thus, a CT scan is not helpful in absolutely excluding many causes, and we are additionally hampered by the lack of a cerebrospinal fluid (CSF) examination, which in the absence of a specific focal lesion on CT would help to exclude a number of possibilities. We can say, however, that disorders such as toxoplasmosis, progressive multifocal leukoencephalopathy, typical or atypical mycobacterial infection, CNS lymphoma and metastatic Kaposi's are quite unlikely, based on CT findings alone.

Because there is no history of meningeal signs such as stiff neck, headache or seizures, one might also exclude meningeal infections such as atypical aseptic meningitis, fungal infections and tuberculous as well as atypical tuberculous infections. It is important to recall, however, that there are documented examples of cryptococcal meningitis in AIDS patients presenting with normal neurologic findings and headache as the only neurologic complaint.[1] With the information at hand, an underlying fungal infection cannot be totally excluded.

We are left, then, with the likely diagnosis of a viral syndrome. Varicella zoster encephalitis in AIDS patients has presented as intractable seizures in a patient recovering from a cryptococcal infection at a time when no evidence of active cryptococcosis could be determined.[1] A patient has also presented with multifocal demyelination,[6] but I will exclude this possibility. Another disorder that encompasses progressive dementia with accompanying motor and behavioral dysfunction has been variously called subacute encephalitis, subacute encephalopathy or, more recently, AIDS-dementia complex.[2,3] The dementia is characterized early on by impaired memory and concentration with psychomotor slowing. Early motor deficits include ataxia, leg weakness, tremor and loss of fine motor coordination. Behavioral disturbances usually include apathy and withdrawal, but may include psychosis. The disease ultimately leaves a patient with severe dementia, mutism, incontinence, paraplegia and occasionally myoclonus. The findings of a CSF analysis are generally nonspecific, and, as noted before, the most common CT finding is cortical atrophy.

As defined by Navia and co-workers,[2,3] the syndrome specifically excludes other conditions such as lymphoma, toxoplasmosis and the like as a cause, but these conditions may coexist. Brain cultures in patients with subacute encephalitis have yielded *Mycobacterium avium-intracellulare,* cytomegalovirus (CMV) and herpes simplex and combinations of the above. It has been suggested that subacute encephalitis or the AIDS-dementia complex is due to CMV infection of the central nervous system.[7] A recent study, however, did not support this conclusion.[2,3] Rather, based on clinicopathologic data, these authors agree that CMV was occasionally an associated infection, while the underlying cause was probably direct brain infection by the AIDS retrovirus or human immunodeficiency virus.

In this case, it would appear that within the limited framework of the signs, symptoms and clinical course described, the patient's condition would best fit the diagnosis of AIDS dementia complex.

DR VINTERS: Autopsy (permission obtained by efforts of R. Mitsuyasu, MD, Division of Hematology-Oncology, UCLA), carried out within 12 hours of death, was restricted to the brain, which weighed 1,170 grams and externally showed no abnormality of the leptomeninges, parenchyma or vasculature. Coronal slices (1 cm) of the fixed cerebral hemispheres similarly showed no abnormality apart from a patchy, ill-demarcated area of grey discoloration in the white matter superior and lateral to the left amygdaloid nucleus, minimal thinning of the corpus callosum and slight enlargement of the lateral ventricles. Horizontal sections of the brain stem and parasagittal sections of cerebellum showed no abnormalities aside from minimal splaying apart of folia, a change restricted to the anterior-superior cerebellar vermis.

Despite the normal appearance of the brain by gross inspection, numerous abnormalities were found on histologic sections. A patchy lymphohistiocytic infiltrate, without microorganisms, was present in the leptomeninges. Throughout the cerebral cortex, there were scattered inflammatory foci consisting primarily of activated microglia—changes usually described (in AIDS patients) by the term microglial nodule encephalitis.[8,9] These focal inflammatory aggregates were especially prominent in the subpial regions (Figure 1) and (less often) deep to the ependyma—that is, they were near the surfaces bathed by CSF. Within these foci but more commonly separate from them and distributed randomly throughout the brain were multinucleate giant cells containing foamy or finely granular cytoplasm (Figure 2). These cells are thought to be a manifestation of direct invasion of the brain by the virus that causes AIDS.[3,10-13] The giant cells were particularly prominent around the adventitia of small blood vessels (Figure 2). (Ultrastructural examination of both cerebrum and cerebellum from this patient has thus far failed to show typical HIV particles within these cells.) Foci of necrotizing encephalitis apparently caused by CMV were seen in several areas, but were especially prominent at the floor of the fourth ventricle in the medulla oblongata (Figure

3) and in the corpus callosum, where typical nuclear and cytoplasmic inclusions of CMV were detected within poorly demarcated foci of demyelination. Many cells bearing typical CMV inclusions in the medulla were also stained with a peroxidase-antiperoxidase procedure for glial fibrillary acidic protein (Figure 4), suggesting that they were of astrocyte origin or reactive ependymal cells[14] previously infected by CMV. Areas of calcified necrotizing leukoencephalopathy were noted in both internal capsules and in the medullary white matter of the right cerebellar hemisphere. These regions showed disruption of axons with neuroaxonal spheroids, lipid-laden macrophages, granular calcification and intense reactive gliosis (Figure 5). There was resultant secondary degeneration of the corticospinal tracts bilaterally. Even in areas not affected by necrotizing leukoencephalopathy, there was intense reactive gliosis with numerous gemistocytic astrocytes within the white matter of the centrum semiovale (Figure 6). Within the cerebellum, in addition to areas of cortical CMV encephalitis (Figure 7), there was patchy but focally pronounced loss of Purkinje's cells with reactive Bergmann's gliosis (Figure 8). In a small segment of cervical spinal cord, vacuolar degeneration of the dorsal columns and corticospinal tracts was seen. Though this showed some similarity to the vacuolar myelopathy described in some AIDS patients,[15,16] the corticospinal tract change might be due to the more proximal capsular leukoencephalopathy, while the dorsal column degeneration may reflect Wallerian degeneration due to disease in the dorsal roots or dorsal root ganglia (these could not be examined because of restrictions on the autopsy).

This case illustrates several important and somewhat controversial issues in understanding the neurologic and neuro-

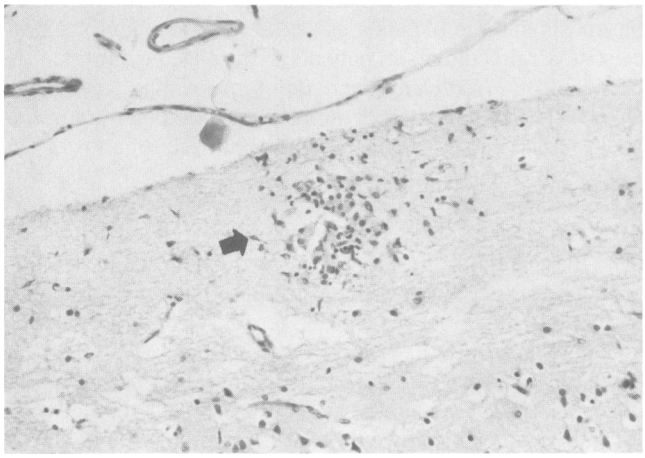

Figure 1.—A section of cingulate gyrus shows an inflammatory (microglial) nodule **(arrow)** in the subpial region (hematoxylin and eosin stain, original magnification × 195).

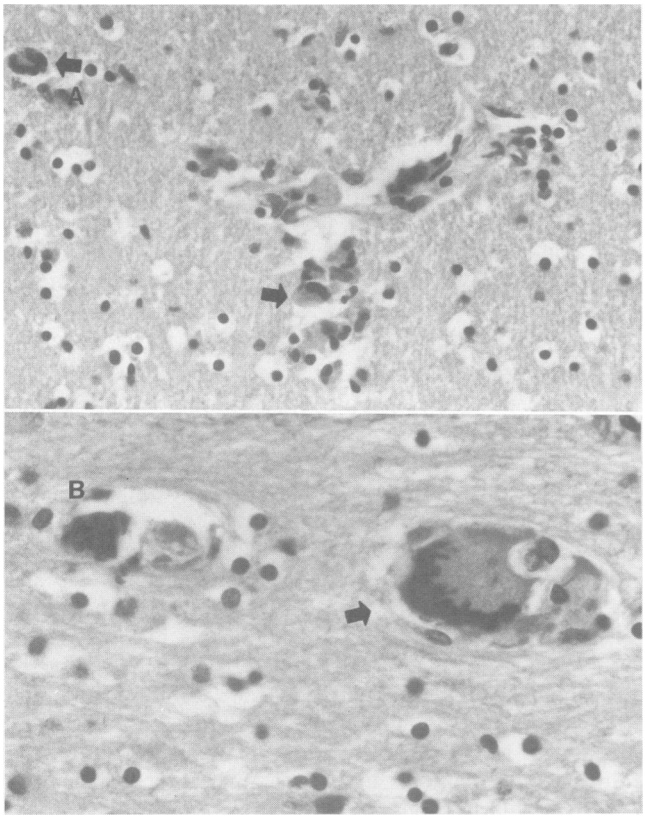

Figure 2.—Multinucleate giant cells **(arrows)** in subcortical white matter of the left frontal lobe **(A)** and in diencephalon **(B)** adjacent to a focus of leukoencephalopathy in the internal capsule (not visible). Giant cells tend to be perivascular and have either little cytoplasm **(A)** or granular/foamy cytoplasm with eccentric nuclei **(B)** (both hematoxylin and eosin stain, **A** original magnification × 500, **B** original magnification × 790).

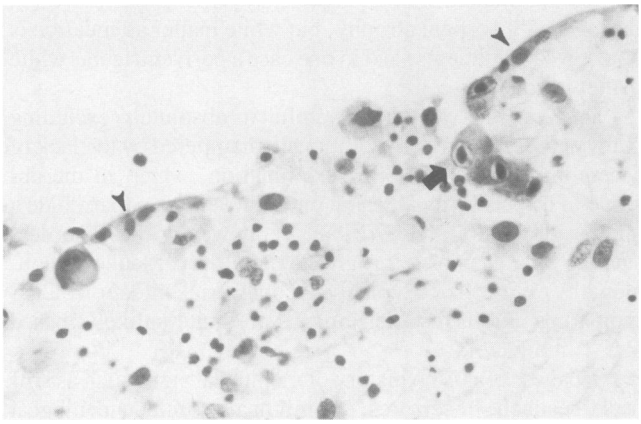

Figure 3.—Cytomegalovirus encephalitis disrupts ependyma **(arrowheads)** of fourth ventricle in medulla. Note typical intranuclear **(arrow)** and cytoplasmic inclusions in ependymal and subependymal cells (hematoxylin and eosin stain, original magnification × 500).

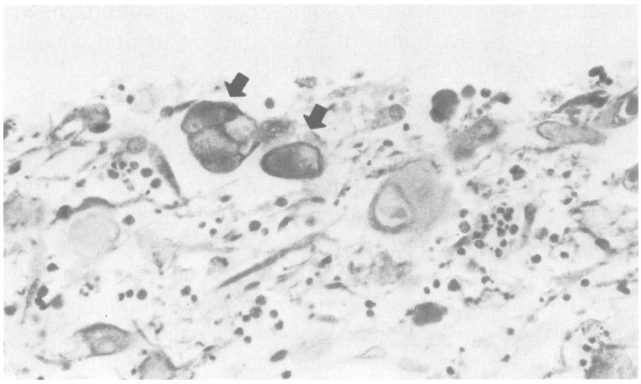

Figure 4.—Subependymal cytomegalovirus inclusion-bearing cells in medulla **(arrows)** show cytoplasmic glial fibrillary acidic protein (GFAP) (peroxidase-antiperoxidase procedure for GFAP, original magnification × 500).

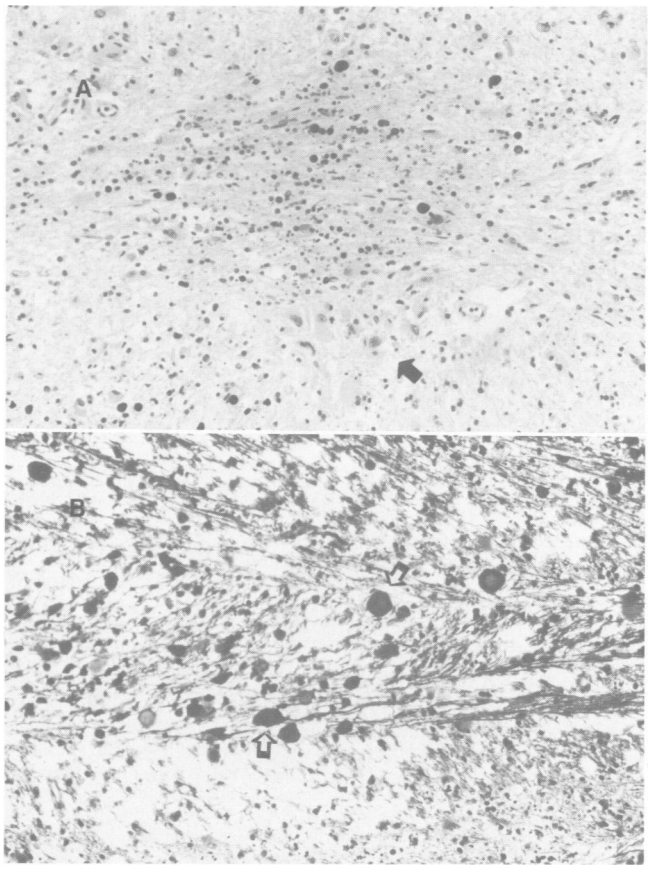

Figure 5.—Necrotizing leukoencephalopathy in right internal capsule shows vacuolation, granular calcification and gliosis **(A).** Arrow points to gemistocytic astrocytes. Evidence of axonal disruption is seen, with prominent neuroaxonal spheroids **(arrows, B)** (**A** hematoxylin and eosin stain, original magnification × 195; **B** Bielschowsky stain, original magnification × 195).

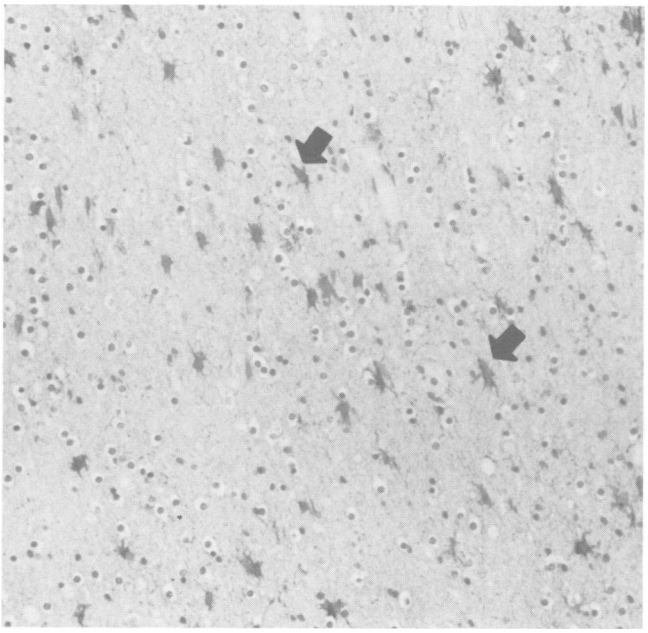

Figure 6.—Left frontal white matter shows reactive hypertrophic gliosis, with prominent astrocytes **(arrows)** (peroxidase-antiperoxidase stain for glial fibrillary acidic protein, original magnification × 195).

pathologic complications of AIDS, particularly AIDS dementia or encephalopathy. The findings in the brain are most consistent with those described by Kleihues and associates[17] in two patients with AIDS, named progressive diffuse leu-

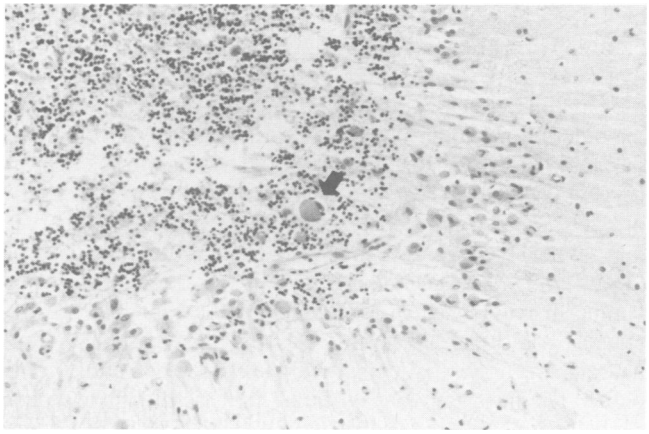

Figure 7.—Focus of cytomegalovirus (CMV) encephalitis in cerebellar vermis. Note severe Purkinje's cell loss and a typical CMV inclusion **(arrow)** (hematoxylin and eosin stain, original magnification × 195).

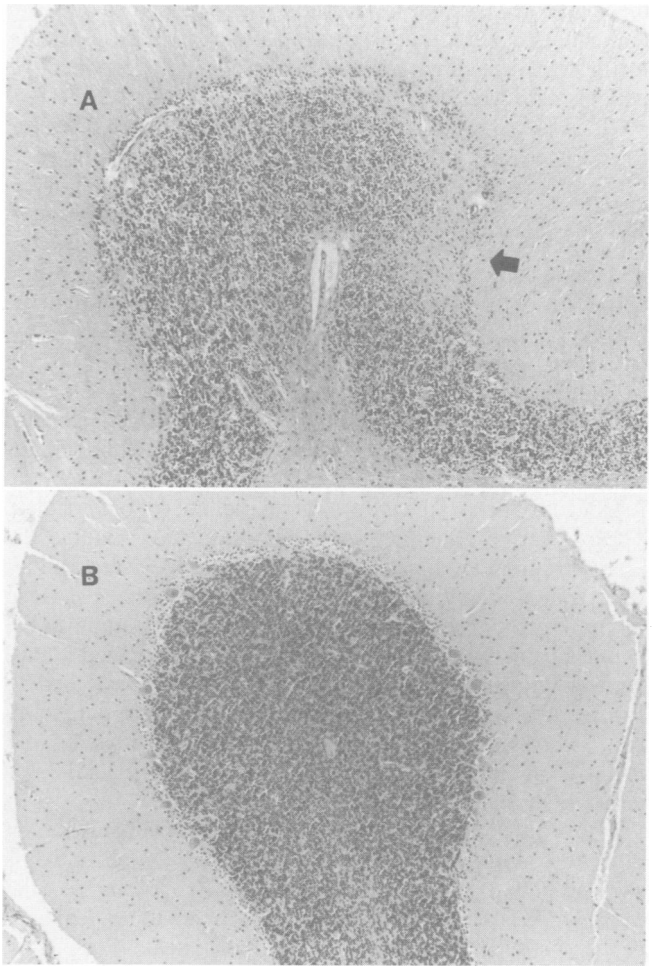

Figure 8.—Cerebellar folia (vermis) from this patient **(A)** and a 52-year-old AIDS patient without ataxia (**B**, control). Note comparatively severe loss of Purkinje's cells and Bergmann's gliosis **(arrow)** in **A** (hematoxylin and eosin stain, both original magnification × 75).

koencephalopathy—that is, leukoencephalopathy more severe in the deep (cerebral and cerebellar) than the subcortical white matter with Wallerian degeneration of long tracts distally, combined with the presence of scattered perivascular giant cells. The latter, as already stated, have been implicated by several investigators as a morphologic hallmark of direct brain infection by HIV. The giant cells have staining features that suggest they are macrophages rather than neuroectodermal cells, but it is unknown whether they originate from the blood or the brain. Several reports now provide evidence that the virus that causes AIDS is to be found in the central nervous system and CSF of patients with neurologic syndromes.[18-22] In rare instances, particles with the ultrastructural appearance of HIV have been seen in the cytoplasm of the previously described giant cells.[10] A recent abstract claims that evidence of HIV infection is found in macrophages, multinucleate cells, astrocytes and basal ganglion neurons of AIDS patients with the AIDS-dementia complex.[23] Kleihues and colleagues felt that the diffuse leukoencephalopathy either was directly related to brain infection by HIV or represented an unusual variant of progressive multifocal leukoencephalopathy caused by papovavirus infection, for which immunohistochemical evidence was presented, though the histologic appearance in both of their cases and in this patient was highly atypical for progressive multifocal leukoencephalopathy.[17] Indeed, lesions of various white matter tracts are common in the brains of a high proportion of patients with AIDS.[9,24-26]

This case is further complicated by the presence of multifocal CMV encephalitis. Areas of the white matter in which CMV was identified frequently showed demyelination of adjacent tracts (such as in the corpus callosum). Others have reported on the association between CMV infection of the nervous system in cases of AIDS and demyelination.[27] Many of the foci of most severe leukoencephalopathy in our patient, however, were clearly remote from zones in which CMV inclusions could be found.

A further intriguing point about this patient is that foci of CMV infection and microglial nodule encephalitis in general were frequently adjacent to surfaces bathed by CSF; for instance, note the severe CMV encephalitis at the base of the fourth ventricle and the numerous subpial microglial nodules. The respective etiologic agents may thus have entered the brain through the blood-CSF barrier (choroid plexus epithelium) rather than crossing the blood-brain barrier, as one might normally expect. CMV infection of the brain in AIDS patients has been shown, by in situ hybridization and immunocytochemical techniques, to seed the ependyma and to spread from there ventriculofugally into the brain parenchyma.[28] The study by Wiley and associates also showed CMV inclusions within cells positive for glial fibrillary acidic protein, which we have confirmed.

Thus the patient's dementia was caused by a combination of diffuse severe leukoencephalopathy, CMV encephalitis and (probable) HIV infection of the brain. Ataxia was the result of CMV encephalitis affecting the cerebellum, leukoencephalopathy affecting the cerebellar white matter and patchy but focally severe loss of Purkinje's cells, most notable in the vermis. The loss of Purkinje's cells may represent yet another direct effect of HIV on the nervous system, though it has not been described in other large series of patients.[1,9,29] Furthermore, it may be attributed to the anoxic-ischemic episodes that this patient almost certainly experienced preterminally.

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